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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,932	12/26/2006	Anjana Rao	10861-033US1	7042

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,932	RAO ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *1-40,42-44 and 46-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/07 and 2/22/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-54 are pending in the application.

Election/Restriction

[2] Applicant's election without traverse of Group VIII, claims 41-45, in the reply filed on 5/16/08 is acknowledged. Applicant's further election without traverse of the species Aip4 and PKCθ in the reply filed on 10/1/08 is acknowledged.

[3] According to applicant, claims 41 and 45 read on the elected species. Claims 1-40, 42-44, and 46-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the replies filed on 5/16/08 and 10/1/08.

Claim to Priority

[4] Applicant's claim for domestic priority under 35 U.S.C. 119(e) to US provisional application 60/512,235, filed on 10/17/03, is acknowledged. The priority claim is set forth in the specification by way of a preliminary amendment filed on 4/14/06.

Information Disclosure Statement

[5] With the exception of references C105-C160, all references cited in the IDSs filed on 8/15/07 and 2/22/08 have been considered by the examiner. A copy of forms PTO-

1449 is attached to the instant Office action. References C105-C160 have not been considered as there is no publication date. See 37 CFR 1.98(b)(5).

[6] If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Specification/Informalities

[7] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Method for Decreasing a Protein-Protein Interaction Between an E3 Ubiquitin Ligase and an E3 Ubiquitin Ligase Substrate---.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[8] Claims 41 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 41 recites “A method for decreasing a protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate…such that the protein-protein interaction between the ligase and the substrate is decreased”. Claim 41 (claim 45 dependent therefrom) is confusing in that, while the claim recites "an E3 ubiquitin

ligase substrate", the claim does not require the presence of the E3 ubiquitin ligase such that a protein-protein interaction can be achieved. While applicant may argue that claim 41 recites "an agent that decreases an interaction between the anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate" and thus requires the presence of an E3 ubiquitin ligase substrate, it is noted that this limitation merely provides a functional description of the "agent" and does not require that the E3 ubiquitin ligase be present with the substrate. Also, the limitation "…such that the protein-protein interaction between the ligase and the substrate is decreased" has been interpreted as an intended use/result of the contacting step, again not requiring the presence of the substrate with the ligase. It is suggested that applicant clarify the meaning of the claim. Because MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation, the claims have been interpreted as not requiring the presence of the E3 ubiquitin ligase substrate. Here, claim 41 has been broadly but reasonably interpreted as requiring only contacting between an "anergy associated" E3 ubiquitin ligase and an agent that decreases interaction.

[b] Claim 41 (claim 45 dependent therefrom) is indefinite in the recitation of "anergy associated E3 ubiquitin ligase" because it is unclear as to what association the ligase must have to anergy to be encompassed within the scope of the claims. Because it is unclear as to what association (direct, indirect, or both?) and what type or kind of association a ligase must have, a skilled artisan would not recognize the intended scope of E3 ubiquitin ligases that are considered to be "anergy associated" and substrates thereof. It is suggested that applicant clarify the meaning of the noted phrase.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[9] Claims 41 and 45 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a method for decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting an anergy associated E3 ubiquitin ligase with an agent that decreases interaction between the anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, optionally wherein the ligase is Aip4 and the substrate is PKCθ. Here, the claims would appear to encompass a naturally-occurring process and thus are directed to non-statutory subject matter. For example, any process whereby the ligase is naturally degraded, which would necessarily decrease interaction between a ligase and its substrate, would be encompassed by the claims. Because the claims read on a process of nature, they should be amended to indicate the hand of the inventor, e.g., by insertion of “isolated” prior to “anergy associated E3 ubiquitin ligase”. See MPEP § 2105.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

> enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[10] Claims 41 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

CLAIM INTERPRETATION: Claim 41 is drawn to a method for decreasing protein-protein interaction between an "anergy associated" E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting an "anergy associated" E3 ubiquitin ligase with a genus of agents that decrease interaction. Claim 45 limits the ligase to Aip4 and the substrate to PKCθ. In view of a broad, but reasonable interpretation of the claims, the structure of the agent is unlimited, and encompasses, *e.g.,* small molecule organic compounds, peptides and polypeptides, and nucleic acids. See specification at pp. 46-51.

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the

variation within the genus. In this case, the specification fails to disclose the reduction to practice of even a single representative species of the genus of "agents". While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Because neither the specification nor the prior art provides a structure-function relationship between an "anergy associated" E3 ubiquitin ligase and an E3 ubiquitin ligase substrate and compounds expected to disrupt a protein-protein interaction between these, it is highly unpredictable as to those compounds that can achieve a decrease in protein-protein interaction. Thus, because the specification fails to disclose a single representative species of such agents and it is highly unpredictable as to which agents would have such activity, the specification fails to adequately describe the genus of "agents".

Given the lack of description of a representative number of "agents", the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[11] Claims 41 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods using an agent that degrades or denatures an E3 ubiquitin ligase, wherein the agent was known at the time of the

invention, does not reasonably provide enablement for methods, including *in vivo* methods, using all "agents" as encompassed by the claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action."

CLAIM INTERPRETATION: As noted above, claim 41 is drawn to a method for decreasing protein-protein interaction between an "anergy associated" E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting an "anergy associated" E3 ubiquitin ligase with an agent that decreases interaction. Claim 45 limits the ligase to Aip4 and the substrate to PKCθ. In view of a broad, but reasonable interpretation of the claims, the structure of the agent is unlimited, and encompasses, *e.g.,* small molecule

organic compounds, peptides and polypeptides, and nucleic acids. See specification at pp. 46-51. Also, it is noted that the process encompasses those using purified ligase, isolated cells expressing the ligase, and *in vivo* methods.

The broad scope of claimed polypeptides is not commensurate with the enablement provided by the disclosure, particularly with respect to the scope of agents that disrupt the protein-protein interaction. In this case, the disclosure is limited to an *in vitro* method, wherein the agent is one that degrades or denatures an E3 ubiquitin ligase, wherein the agent was know at the time of the invention.

(B) The nature of the invention: The nature of the invention appears to be in the finding that E3 ubiquitin ligases mediate degradation of calcium and calcineurin signaling molecules, which results in anergy (antigen unresponsiveness) in T cells (see, *e.g.,* specification at pp. 72-75).

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: According to MPEP 2164.03, "…what is known in the art provides evidence as to the question of predictability." Here, the prior art does not appear to expressly disclose any specific "agents" that decrease protein-protein interaction between an E3 ubiquitin ligase and its substrate. However, since an E3 ubiquitin ligase would need to maintain a proper three-dimensional conformation for catalytic activity, one of skill in the art would recognize that an agent that denatured or degraded an E3 ubiquitin ligase would be one that necessarily reduced protein-protein interaction with respect to its substrate.

(F) The amount of direction provided by the inventor and (G) The existence of working examples: The specification fails to disclose even a single working example of an "agent" as recited in the claims, only general assays that *may* result in identification of such an "agent".

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While *in vitro* methods for identifying agents that disrupt a protein-protein interaction were known in the art at the time of the invention, there is no way to determine the quantity of experimentation required because the specification fails to disclose such a compound and one has no expectation of obtaining such a compound.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[12] Claim(s) 41 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Wood et al. (*Mol. Cell. Neurosci.* 11:149-160, 1998; "Wood").

CLAIM INTERPRETATION: Claim 41 is drawn to a method for decreasing protein-protein interaction between an "anergy associated" E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting an "anergy associated" E3 ubiquitin ligase with an agent that decreases interaction. Claim 45 limits the ligase to Aip4 and the substrate to PKCθ. As noted above, claim 41 does not require the presence of the E3 ubiquitin ligase substrate. Although claim 41 recites the limitation "…that decreases an interaction between the anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate…", this has been interpreted as a functional feature of the agent and not requiring the presence of the substrate with the ligase. Also, the limitation "…such that the protein-protein interaction between the ligase and the substrate is decreased" has been interpreted as an intended use/result of the contacting step, again not requiring the presence of the substrate with the ligase. Here, claim 41 has been broadly but

reasonably interpreted as requiring only contacting between an “anergy associated” E3 ubiquitin ligase and an agent that decreases interaction.

The reference of Wood teaches an Aip4 protein with an N-terminal GST fusion moiety and treating the fusion polypeptide with SDS and analyzing the protein by SDS-PAGE (p. 152, Figure 3 and p. 158, paragraph bridging columns 1-2). Because SDS is a known protein denaturant, it is considered to be an "agent" as encompassed by the claims because it would necessarily decrease protein interaction. This anticipates claims 41 and 45.

Conclusion

[13] Status of the claims:

- Claims 1-54 are pending.
- Claims 1-40, 42-44, and 46-54 are withdrawn from consideration.
- Claims 41 and 45 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656